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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,884	04/07/1999	HAROLD J. WANEBO	58463/JPW/EM	6824

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
08/21/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/287,884	WANEBO ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-29,31-33 and 42-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-29,31-33 and 42-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 6/9/2009, are acknowledged and entered. Claim 30 has been cancelled by Applicant. Claims 20-29, 31-33, and 42-54 are pending and under examination.

Upon further consideration, the indication of allowable subject matter set forth in the Advisory Action mailed 4/13/2009 is hereby **withdrawn**. As discussed with the attorney of record, Tish DeGrasse, Applicant's demonstration of unexpected results is not commensurate in scope with the patent protection sought by the pending claims. Applicants have only demonstrated a synergistic effect when C_6-ceramide is present in a much higher amount than paclitaxel (*e.g.*, a ratio of 41.7:1 to 4167:1). Whether such synergism occurs in ratios outside this range, or when paclitaxel is present in a higher amount than C_6-ceramide has not been demonstrated and there is not factual evidence in the present application that such would be case. Accordingly, previously applied 35 U.S.C. 103 rejections are herein reapplied against the pending claims. Favorable consideration would be given to claims limited to administration of C_6-ceramide and paclitaxel in a ratio of 41.7:1 to 4167:1.

In light of the new rejections being applied against the pending claims, the finality of the Office Action mailed 12/4/2008 is hereby **withdrawn**. Accordingly, the Notice of Appeal filed 6/9/2009 is deemed **moot** in light of the reopening of prosecution.

Response to Arguments

Any previous rejections and/or objections to claim 30 are withdrawn as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 6/9/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Declaration under Rule 1.132

The Examiner acknowledges receipt of the Rule 1.132 Declaration of Harold Wanebo ("Wanebo" Declaration) and has carefully considered the information provided therein.

Claim Interpretation

The instant claims comprise contacting head and neck squamous cell or pancreatic cancer cell comprising tumors with "an amount of paclitaxel" and "an amount of C6-ceramide", wherein the amount of paclitaxel and C6-ceramide in combination are effective to induce at least 50% growth inhibition. Accordingly, the claims encompass embodiments wherein paclitaxel is administered in an amount that induces at least 50% growth inhibition alone, and "an amount" of C6-ceramide (*e.g.*, 0.0001 mg) is also administered with paclitaxel.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-29, 31-33, and 42-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Spencer *et al***. (Drugs, 1994, vol. 48, pages 794-847) (prior art of record) in view of **Jayadev *et al***. (J. Biol. Chem., 1995, vol. 270, pages 2047-2052) (prior art of record).

The central issue remaining in the present case is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat head and neck squamous carcinoma cells or pancreatic cancer cells. The Examiner believes that a *prima facie* case of obvious is established by the following prior art references.

Spencer *et al*. teach that paclitaxel has demonstrated broad-spectrum anticancer activity, including activity in treating the specific cancers recited in the instant claims (Table 1). The values presented in Table 1 are IC_{50} values, which are amounts required to produce 50% inhibition or death of human cancer cells *in vitro*. In this regard, it is noted that the IC_{50} of paclitaxel against head and neck squamous cell carcinomas was <0.001 nmol/L and against pancreatic carcinomas cells was 3-60 nmol/L (Table 1). At page 807, left column, Spencer teaches that the activity of paclitaxel *in vivo* against human tumor xenografts and murine tumors was "consistent with *in vitro* results". In this regard, intravenous paclitaxel 12 or 24 mg/kg inhibited growth of human pancreatic tumors by 80% (page 808, right column). Thus, Spencer et al. disclose that amounts of paclitaxel exist which induce 50% growth inhibition of tumor cells as recited in the instant claims.

Regarding combination therapy, Spencer et al. disclose that paclitaxel is often administered with other anticancer agents, including cisplatin, cyclophosphamide, doxorubicin, hydroxyurea and dexamethasone (pages 798-799, 805-806 and 821-826). Such combinations are often synergistic. With respect to *in vivo* administration, tumor growth inhibition, decreasing size of tumors, and administration routes as recited in the instant claims, such *in vivo* administration of paclitaxel to subjects having tumors is taught at page 807, “Activity In Vivo". “[C]remophore-mediated delivery” as recited in claims 23, 28, 45, and 50 is taught at page 807, right column, first full paragraph and page 837, right column). Intraperitoneal and subcutaneous administration as recited in claims 24, 29, 46, and 51 is taught at page 807, right column, second full paragraph and pages 837-838, “Dosage and Administration”.

Spencer et al. thus teach using paclitaxel as a chemotherapeutic agent for the treatment of such cancers as head and neck squamous cell carcinomas and pancreatic cancer, both alone as a single agent and in combination with other chemotherapeutic agents. Spencer et al. differ from the instant claims in that they do not disclose C6-ceramide.

However, Jayadev *et al*. teach that C_6-ceramide causes apoptosis in Molt-4 leukemia cells through significant G_0/G_1 arrest (Abstract). The reference also teaches that the effects of C_6-ceramide on cell cycle arrest are a generalized phenomenon, not restricted to the Molt-4 cell line (page 2049).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer paclitaxel in combination with C_6-ceramide as taught by Spencer et al. in view of the teachings of Jayadev *et al*. One would have been motivated to do so because each of the therapeutics have been individually taught in the prior art to be successful at treating cancer, and further, Spencer *et al*. motivates combination therapy for the treatment of cancer using paclitaxel and a second therapeutic agent. Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering paclitaxel in combination with C_6-ceramide as taught by Spencer et al. in view of the teachings of Jayadev *et al*., one would achieve a method of treating cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In fact, Applicants recognize this motivation to combine wherein they state that paclitaxel combined with other chemotherapeutic agents in the treatment of a variety of cancers, including leukemia, typically produces a stronger tumor cell growth inhibition than a single chemotherapeutic agent (page 2, lines 21-26 of specification).

Accordingly, the claims are deemed properly rejected under 35 U.S.C. § 103 as being obvious over Spencer et al. in view of Jayadev *et al*. As discussed *supra*, it is the Examiner's position that the unexpected results are not commensurate in scope with the patent protection sought by Applicants. Applicants have only demonstrated a synergistic effect when C_6-

ceramide is present in a much higher amount than paclitaxel (*e.g.*, a ratio of 41.7:1 to 4167:1). Whether such synergism occurs in ratios outside this range, or when paclitaxel is present in a higher amount than C_6-ceramide has not been demonstrated and there is no factual evidence in the present application that such would be case.

Claims 20-29, 31-33, and 42-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Spencer *et al***. (Drugs, 1994, vol. 48, pages 794-847) (prior art of record) in view of **Cai *et al***. (J. Biol. Chem., 1997, vol. 272, pages 6918-6926) (prior art of record).

Spencer *et al*. teach that paclitaxel has demonstrated broad-spectrum anticancer activity, including activity in treating the specific cancers recited in the instant claims (Table 1). The values presented in Table 1 are IC_{50} values, which are amounts required to produce 50% inhibition or death of human cancer cells *in vitro*. In this regard, it is noted that the IC_{50} of paclitaxel against head and neck squamous cell carcinomas was <0.001 nmol/L and against pancreatic carcinomas cells was 3-60 nmol/L (Table 1). At page 807, left column, Spencer teaches that the activity of paclitaxel *in vivo* against human tumor xenografts and murine tumors was "consistent with *in vitro* results". In this regard, intravenous paclitaxel 12 or 24 mg/kg inhibited growth of human pancreatic tumors by 80% (page 808, right column). Thus, Spencer et al. disclose that amounts of paclitaxel exist which induce 50% growth inhibition of tumor cells as recited in the instant claims.

Regarding combination therapy, Spencer et al. disclose that paclitaxel is often administered with other anticancer agents, including cisplatin, cyclophosphamide, doxorubicin, hydroxyurea and dexamethasone (pages 798-799, 805-806 and 821-826). Such combinations are often synergistic. With respect to *in vivo* administration, tumor growth inhibition, decreasing size of tumors, and administration routes as recited in the instant claims, such *in vivo* administration of paclitaxel to subjects having tumors is taught at page 807, “Activity In Vivo". “[C]remophore-mediated delivery” as recited in claims 23, 28, 45, and 50 is taught at page 807, right column, first full paragraph and page 837, right column). Intraperitoneal and subcutaneous administration as recited in claims 24, 29, 46, and 51 is taught at page 807, right column, second full paragraph and pages 837-838, “Dosage and Administration”.

Spencer et al. thus teach using paclitaxel as a chemotherapeutic agent for the treatment of such cancers as head and neck squamous cell carcinomas and pancreatic cancer, both alone as a single agent and in combination with other chemotherapeutic agents. Spencer et al. differ from the instant claims in that they do not disclose C6-ceramide.

Cai *et al*. teach that C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells (pages 6922-6923; Figure 5).

While the skilled artisan cannot, *a priori*, predict whether a given combination of drugs will have an additive, synergistic, or antagonistic effect, the skilled artisan would reasonably expect that two anticancer agents would, when combined, be effective to treat cancer. As such, it is, even in the absence of any explicit teachings, *prima facie* obvious to combine two agents known to treat cancer.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer C_6-ceramide in combination with paclitaxel as taught by Spencer *et al*. in view of the teachings of Cai *et al*. One would have been motivated to do so because each of the therapeutics have been individually taught in the prior art to be successful at treating cancer, and further, Spencer *et al*. motivates combination therapy for the treatment of cancer using paclitaxel and a second therapeutic agent. Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering C_6-ceramide in combination with paclitaxel as taught in Spencer *et al*. in view of the teachings of Cai *et al*., one would achieve a method of treating cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In fact, Applicants recognize this motivation to combine wherein they state

that paclitaxel combined with other chemotherapeutic agents in the treatment of a variety of cancers, including leukemia, typically produces a stronger tumor cell growth inhibition than a single chemotherapeutic agent (page 2, lines 21-26 of specification).

Accordingly, the claims are deemed properly rejected as being obvious over Spencer *et al*. in view of Cai *et al*. The skilled artisan would have been imbued with at least a reasonable expectation that a combination of paclitaxel and C_6-ceramide would be effective in treating cancer. As discussed *supra*, it is the Examiner's position that the unexpected results are not commensurate in scope with the patent protection sought by Applicants. Applicants have only demonstrated a synergistic effect when C_6-ceramide is present in a much higher amount than paclitaxel (*e.g.*, a ratio of 41.7:1 to 4167:1). Whether such synergism occurs in ratios outside this range, or when paclitaxel is present in a higher amount than C_6-ceramide has not been demonstrated and there is no factual evidence in the present application that such would be case.

Claims 20-29, 31-33, and 42-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Spencer *et al***. (Drugs, 1994, vol. 48, pages 794-847) (prior art of record) in view of **Wei *et al***. (USP No. 5,631,394; Issued May 20, 1997) (newly cited).

The central issue remaining in the present case is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat head and neck squamous carcinoma cells or pancreatic cancer cells. The Examiner believes that a *prima facie* case of obvious is established by the following prior art references.

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et al. disclose that amounts of paclitaxel exist which induce 50% growth inhibition of tumor cells as recited in the instant claims.

Regarding combination therapy, Spencer et al. disclose that paclitaxel is often administered with other anticancer agents, including cisplatin, cyclophosphamide, doxorubicin, hydroxyurea and dexamethasone (pages 798-799, 805-806 and 821-826). Such combinations are often synergistic. With respect to *in vivo* administration, tumor growth inhibition, decreasing size of tumors, and administration routes as recited in the instant claims, such *in vivo* administration of paclitaxel to subjects having tumors is taught at page 807, "Activity In Vivo". "[C]remophore-mediated delivery" as recited in claims 23, 28, 45, and 50 is taught at page 807, right column, first full paragraph and page 837, right column). Intraperitoneal and subcutaneous administration as recited in claims 24, 29, 46, and 51 is taught at page 807, right column, second full paragraph and pages 837-838, "Dosage and Administration".

Spencer et al. thus teach using paclitaxel as a chemotherapeutic agent for the treatment of such cancers as head and neck squamous cell carcinomas and pancreatic cancer, both alone as a single agent and in combination with other chemotherapeutic agents. Spencer et al. differ from the instant claims in that they do not disclose C6-ceramide.

However, Wei *et al*. teach that increases in ceramide concentrations can stimulate apoptosis (col. 2, lines 13-29) and demonstrate that C_6-ceramide inhibits the growth of human and mouse cancer cell lines *in vitro* with GI_{50} values ranging from 7.0 to 36 μM (Table 4).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer paclitaxel in combination with C_6-ceramide as taught by Spencer et al. in view of the teachings of Wei *et al*. One would have been motivated to do so because each of the therapeutics have been individually taught in the prior art to be successful at treating cancer and/or inhibiting cancer cell growth, and further, Spencer *et al*. motivates combination therapy for the treatment of cancer using paclitaxel and a second therapeutic agent. Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to

the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering paclitaxel in combination with C_6-ceramide as taught by Spencer et al. in view of the teachings of Wei *et al*., one would achieve a method of treating cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In fact, Applicants recognize this motivation to combine wherein they state that paclitaxel combined with other chemotherapeutic agents in the treatment of a variety of cancers, including leukemia, typically produces a stronger tumor cell growth inhibition than a single chemotherapeutic agent (page 2, lines 21-26 of specification).

Accordingly, the claims are deemed properly rejected under 35 U.S.C. § 103 as being obvious over Spencer et al. in view of Wei *et al*. As discussed *supra*, it is the Examiner's position that the unexpected results are not commensurate in scope with the patent protection sought by Applicants. Applicants have only demonstrated a synergistic effect when C_6-ceramide is present in a much higher amount than paclitaxel (*e.g*., a ratio of 41.7:1 to 4167:1). Whether such synergism occurs in ratios outside this range, or when paclitaxel is present in a higher amount than C_6-ceramide has not been demonstrated and there is no factual evidence in the present application that such would be case.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614